THE XXth CENTURY DENGUE PANDEMIC: NEED FOR SURVEILLANCE AND RESEARCH

Scott B. Halstead*

History of dengue

The evolutionary history of the dengue viruses and their involvement with human beings is obscure. Because there is a well-established zoontic cycle in which South-East Asian subhuman primates support the efficient transmission of all four dengue serotypes, it is tempting to view this geographical region as the "home" of the dengue viruses (1). In Asia, the urban cycle, involving Aedes aegypti and human beings, probably started when Western trade and colonial expansion introduced the vector from Africa (2). Scientific dengue virology had to await the isolation in mice of types 1 and 2 in the 1940s (3, 4). Except for several retrospective serological studies (5, 6), epidemics before 1940 must be surmised from their clinical and epidemiological characteristics.

Using these identifying features, dengue viruses appear to have spread outside their ancestral home in pandemic fashion in each of the past two centuries. The tip of an XVIIIth century pandemic can be identified from the classic description of dengue fever in Philadelphia in 1780 by Benjamin Rush (7). The causal virus and transmitting mosquito undoubtedly were introduced into Philadelphia by ship, an unwelcome consequence of the sugar, rum and slave trade between African, colonial American and Caribbean ports. This first pandemic produced reports of sporadic dengue outbreaks in the United States of America, Caribbean and South American coastal cities during the XIXth century and the first three decades of the XXth century (8).

A second pandemic had its most obvious locus in semi-tropical northern Queensland where gold and sugar generated rapid population growth. Settlers lived in hastily constructed boom towns depending for water on rain collected from roof runoff and stored in rain barrels. The resultant Aedes aegypti populations supported continuous dengue activity in Australia from the 1870s until World War I (9). The first outbreak of a disease resembling dengue haemorrhagic fever/dengue shock syndrome (DHF/DSS) was reported from Charters Towers and nearby towns in 1897 (10). Dengue-like epidemics were also reported from the eastern Mediterranean in the late XIXth century (11), culminating in the explosive and severe Greek epidemic of 1928 (12). Effective mosquito control measures introduced in Greece and in many colonial cities in tropical Asia, as well as the anti-Aedes campaigns of the American hemisphere, produced a global interregnum in dengue transmission in the mid-XXth century (13).

Modern pandemic dengue

The great XXth century pandemic grew out of ecological forces brought into play by World War II and which have continued at unprecedented levels since then. Early in the war, dengue strains were carried by combatants from South-East Asia to Japan and the Pacific Islands, including Hawaii. Little is known about the distribution of dengue serotypes prior to World War II, but there is no question that destruction of city water supplies, temporary housing for war refugees, the explosive post-war growth of populations through high fertility and rural-to-urban migration, and the steady deterioration of urban environments, have led to sustained growth in density and the area occupied by Aedes aegypti. Together these factors have resulted in the endemic transmission of all four dengue serotypes in most of the Asian tropics. With almost no effective programmes of vector containment, absolute numbers of dengue infections, as well as dengue infection rates, have increased steadily over the past 40 years. Meanwhile, the remarkable gains achieved towards the eradication of Aedes aegypti in the American tropics have been eroded and reversed. This was followed by the introduction and spread of dengue viruses beginning in the 1960s. Where once they were absent, dengue viruses have invaded Cuba, many of the Caribbean Islands, Mexico, the United States, most of Central America, Colombia, Ecuador, Peru, Paraguay, Bolivia, Argentina and Brazil (Maps 1 & 2). By the 1990s dengue had spread north to China, including the province of Taiwan, and south to Queensland (Australia) and repeatedly eastward to nearly all of the Pacific Islands, most conspicuously Tahiti. In Africa and the Middle East, areas of epidemic activity include outbreaks in Kenya, Mozambique, Somalia and Yemen (Map 3).

The haemorrhagic fever phenomenon

The most important attribute of the XXth century dengue pandemic has not been its extent, but its intensity. Repeated serological studies have shown that 3 or 4 dengue serotypes have been simultaneously or serially endemically transmitted in all of the Asian tropics, probably since at least the 1960s, and also in the American tropics with the progressive spread of Aedes aegypti there beginning in the 1970s. In South-East Asia this hyperendemicity resulted in a new acute vascular permeability syndrome, the dengue haemorrhagic fever/dengue shock syndrome (DHF/DSS). Limited mainly to children, DHF/DSS results in hypovolemic shock, often complicated by severe internal haemorrhaging and a high case-fatality rate.

We now know that beginning slowly in the early 1950s, children with dengue haemorrhagic fever were being hospitalized in Thailand (14). Clusters of cases were identified in Manila in 1954, and longer outbreaks in Manila in 1956 and Bangkok in 1958 (14). Absolute numbers of recorded cases of DHF/DSS have increased dramatically since 1960 parallel ing, but not completely concordant with, the endemicity of two or more dengue viruses. Case attack

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Rates have shown similar dramatic increases. DHF/DSS has spread throughout tropical Asia and is now endemic in all countries of the region with the exception of Bangladesh, India and Pakistan. Table 1 details case reports for the past 30 years. Cases and deaths are grouped by the 20-year period, 1961-1980, then two 5-year periods, 1981-1985 and 1985-1990. Cases in the latter two time-periods equal or exceed those reported during the first 20 years of epidemic DHF/DSS. Major recent extensions include the Cuban outbreak of 1981, southern China and Hainan Island (15), Sri Lanka (16), India (17), Maldives (S. Nimmannitya, personal communication), Tahiti (18) and Venezuela (19) in the mid- to late 1980s. Although there is limited or no reporting, there can be little doubt that the Lao People’s Democratic Republic and Cambodia have experienced DHF/DSS at the same high level of endemicity as neighbouring Thailand and Viet Nam.

Cases reported to the Western Pacific and South-East Asia Regional Offices of the World Health Organization require some comment. Notification of DHF/DSS cases to WHO by Member States is voluntary. Largely due to the work of the interregional Technical Advisory Committee on Dengue and Den-
gue Haemorrhagic Fever which has met at frequent intervals since 1973, a case definition of DHF/DSS was adopted and guides to diagnosis, treatment and control of the disease prepared (20). The Technical Guide provided a case notification form and, as recommended, the two regions have been served by a Dengue Newsletter. The request to Member States from WHO is that hospitalized cases and deaths, shock and non-shock, be reported monthly, giving age and sex. In practice, cases are reported annually: several countries have extended their own national case reporting to include hospital outpatients. DHF/DSS case reporting is incomplete (Cambodia, Lao P. D. R.), fails to conform to WHO case definitions (most countries) and is inflated (most countries). Few countries report DSS separately from DHF, non-shock. Many mix dengue fever cases with DHF/DSS. Overreporting of DHF/DSS is a problem, but it is not yet known what proportion of the increase in DHF/DSS cases is attributable to inflation in the reporting base.

Distribution of DHF/DSS: implications for pathogenesis

A glance at the world map (Map 3) shows heterogeneous disease distribution. The circulation of multiple dengue serotypes does not always produce DHF/DSS. This includes all of Africa and much of tropical America.

Why should this be? Observations made during the 1981 dengue outbreak in Cuba established the fact that blacks are relatively resistant to DHF/DSS (21). A resistance gene in blacks might account for the absence of reports of DHF/DSS from Africa where dengue 2 and 3 have been epidemic while type 2 is enzootic in West African subhuman primates (22, 23). What is less clear is whether a resistance gene widely distributed in tropical American populations accounts for the relative paucity of DHF/DSS in this hemisphere. Virological studies related to the Cuban epidemic and the recent sharp DHF/DSS outbreak in

### TABLE 1. DENGUE HAEMORRHAGIC FEVER CASES (AND DEATHS) REPORTED TO WHO REGIONAL OFFICES, 1956-1990

<table>
<thead>
<tr>
<th>Year</th>
<th>Philippines</th>
<th>Viet Nam</th>
<th>China</th>
<th>Thailand</th>
<th>Lao P.D.R.</th>
<th>Cambodia</th>
<th>Myanmar</th>
<th>Malaysia</th>
</tr>
</thead>
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<tr>
<td>1956-1980</td>
<td>25,831</td>
<td>2,124</td>
<td>325,409</td>
<td>6,268</td>
<td>36,256</td>
<td>2,456</td>
<td>23,566</td>
<td>5,926</td>
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<tr>
<td>1981</td>
<td>123</td>
<td>8</td>
<td>35,523</td>
<td>409</td>
<td>25,641</td>
<td>194</td>
<td>1,524</td>
<td>90</td>
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<tr>
<td>1982</td>
<td>305</td>
<td>31</td>
<td>39,806</td>
<td>361</td>
<td>22,250</td>
<td>159</td>
<td>49</td>
<td>3,052</td>
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<tr>
<td>1983</td>
<td>1,684</td>
<td>130</td>
<td>149,519</td>
<td>1,796</td>
<td>85,293</td>
<td>3,032</td>
<td>30,022</td>
<td>231</td>
</tr>
<tr>
<td>1984</td>
<td>2,546</td>
<td>89</td>
<td>30,498</td>
<td>386</td>
<td>69,597</td>
<td>481</td>
<td>22</td>
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<td>1985</td>
<td>4,517</td>
<td>209</td>
<td>29,450</td>
<td>486</td>
<td>80,076</td>
<td>542</td>
<td>1,759</td>
<td>15</td>
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<tr>
<td>1986</td>
<td>867</td>
<td>101</td>
<td>46,266</td>
<td>511</td>
<td>29,030</td>
<td>206</td>
<td>365</td>
<td>43</td>
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<tr>
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<td>859</td>
<td>27</td>
<td>30,517</td>
<td>1,566</td>
<td>170,630</td>
<td>896</td>
<td>3,914</td>
<td>91</td>
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<tr>
<td>1988</td>
<td>2,922</td>
<td>68</td>
<td>85,160</td>
<td>826</td>
<td>51,510</td>
<td>1,259</td>
<td>26,926</td>
<td>189</td>
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<tr>
<td>1989</td>
<td>305</td>
<td>14</td>
<td>40,205</td>
<td>285</td>
<td>37,996</td>
<td>907</td>
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<td>280</td>
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<tr>
<td>1990</td>
<td>588</td>
<td>27</td>
<td>37,569</td>
<td>255</td>
<td>38,062</td>
<td>2,626</td>
<td>113,655</td>
<td>422</td>
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<tr>
<td>1981-1985</td>
<td>4,657</td>
<td>258</td>
<td>300,253</td>
<td>3,334</td>
<td>85,293</td>
<td>3,032</td>
<td>227,586</td>
<td>1,577</td>
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<tr>
<td>1986-1990</td>
<td>5,361</td>
<td>166</td>
<td>563,717</td>
<td>3,447</td>
<td>127,568</td>
<td>4,792</td>
<td>409,645</td>
<td>1,993</td>
</tr>
<tr>
<td>Total</td>
<td>35,849</td>
<td>2,548</td>
<td>1,189,379</td>
<td>13,049</td>
<td>249,117</td>
<td>10,279</td>
<td>873,787</td>
<td>9,496</td>
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Rapp. trimest. statist. sanit. mond., 45 (1992)
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Need for better surveillance and more research

The almost unnoticed DHF/DSS outbreak in New
Delhi in 1988 is a sad reflection on the readiness and
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Still not understood are differences between viruses
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terest now shifts to Africa where epidemiological studies of dengue infection are crucial.

Understanding the pathogenesis of DHF/DSS is still a major public health challenge and a first-rate scientific problem. One of the most exciting research opportunities is to uncover the molecular bases for resistance to dengue disease severity in blacks. This discovery could unlock many secrets. This problem cries out for immediate attention. Essential to any studies is the recovery of viral strains representative of initial infecting viruses and of those producing DHF/DSS. This can be accomplished only through prospective studies in which there is careful documentation of dengue clinical syndromes and the recovery and preservation of dengue strains. WHO technical advisory groups have repeatedly called for such studies and for the conservation of viral strains in regional laboratory facilities. Never before has implementation of these recommendations been so urgent.

In 1980 the Bulletin of the World Health Organization published a status report on dengue haemorrhagic fever which called for improved research and improved surveillance by laboratories serving populations in which dengue viruses were active (14). Fortunately, several crucial research questions have been answered, but these have led to a set of new research questions. Because the XXth century dengue pandemic shows no sign of waning, an even larger portion of the world's population is at risk to DHF/DSS. It is essential to establish improved clinical and virological surveillance designed to answer crucial research questions, particularly in areas at risk to the introduction of dengue haemorrhagic fever.

SUMMARY

By the last decade of the XXth century Aedes aegypti and the 4 dengue viruses had spread to nearly all countries of the tropical world. Some 2 billion persons live in dengue-endemic areas with tens of millions infected annually. Dengue pandemics were also documented in the XVIIIth and XIXth centuries; they were contained by organized anti-Aedes aegypti campaigns and urban improvements. The XXth century dengue pandemic has brought with it the simultaneous circulation of multiple serotypes and in its aftermath, endemic dengue haemorrhagic fever/dengue shock syndrome (DHF/DSS). Nearly 3 million children have been hospitalized with this syndrome in the past 3 decades, mainly in South-East Asia. Recent outbreaks of DHF/DSS in the Pacific Islands, China, India, Sri Lanka, Cuba and Venezuela are indicators of the high intensity and rapid spread of dengue transmission. The magnitude of the XXth century dengue pandemic requires urgent improvements in early warning surveillance by WHO Member States and the development of the capacity to study underlying mechanisms of the disease.

A key research question is why does DHF/DSS not occur with all second dengue infections? Two answers have been suggested: (1) a human resistance gene. Data from the 1981 DHF/DSS epidemic in Cuba have demonstrated the existence in blacks of a resistance gene. The effect of such a gene in reducing disease susceptibility of American and African blacks requires more study. (2) The existence of dengue "biotypes". Some, but not all biotypes may cause DHF/DSS during a second dengue infection. A South-East Asian dengue 2 biotype introduced into Cuba is thought to be responsible for the 1981 DHF/DSS epidemic. DHF/DSS did not occur with the genetically distinct Caribbean dengue 2 viruses which were in circulation in the 1970s.

How does a second dengue infection cause severe disease? A recent study in Thailand suggests that when antibody residual from the first infection is able to neutralize a second virus type, even weakly, a secondary infection will occur, but its severity is down-regulated and the disease mild. When no cross-reactive neutralizing antibodies are raised, a second infection is under the influence of enhancing antibody; the resulting infection and disease are severe. The presence or absence of antibodies on both the first and second virus determine disease severity. An alternate mechanism which could determine disease severity is that South-East Asian dengue viruses may be inherently more capable of supporting severe antibody-enhanced infection than viruses from other geographical regions.

The extension of DHF/DSS to new areas always provides opportunities to study and understand disease pathogenesis. Two very important elements of dengue control are lacking in most countries, namely enhanced surveillance for DHF/DSS and improved research which should include at least the study of pre- and post-epidemic sera and the isolation of viruses from serologically documented cases.

RÉSUMÉ

La pandémie de dengue du XXe siècle: besoin de surveillance et de recherche

La dernière décennie du XXe siècle a vu Aedes aegypti et les 4 virus de la dengue s'étendre à presque tous les pays du monde tropical. Cela a été observé dans plusieurs dizaines de millions d'entre elles. Des pandémies de dengue avaient déjà été observées aux XVIIIe et XIXe siècles: elles ont été endiguées grâce à
des campagnes de démolitions dirigées contre Aedes aegypti et à l'amélioration de l'urbanisme. La pandémie de dengue du XXe siècle a mis simultanément en circulation de multiples sérotypes et, dans son sillage, la dengue endémique et sa forme hémorragique avec syndrome de choc. Près de 3 millions d'enfants présentant ce syndrome ont été hospitalisés au cours des 3 décennies écoulées, principalement en Asie du Sud-Est. Les flambées qui ont éclaté récemment dans les îles du Pacifique, en Chine, en Inde, au Sri Lanka, à Cuba et au Venezuela montrent combien la transmission de la dengue est intense et sa propagation rapide. L'amplificateur de la pandémie actuelle exige qu'on améliore de toute urgence le système de veille avancée mis en place par l'OMS et ses États Membres et qu'on se donne les moyens d'étudier la pathogénie de la maladie.

Un point crucial pour la recherche est de savoir pourquoi la maladie ne se produit pas toujours après une deuxième infection. On a proposé deux réponses: 1) l'existence d'un gène de résistance chez l'homme. Les données tirées de l'épidémie de 1981 qui s'est produite à Cuba ont permis de mettre en évidence l'existence d'un gène de résistance chez les Noirs. Il convient d'étudier de façon plus approfondie l'effet qu'un tel gène pourrait avoir sur la réduction de la sensibilité à la maladie chez les Noirs d'Amérique et d'Afrique. 2) l'existence de «biotypes» de la dengue. Certains biotypes, mais pas tous, pourraient entrainer une dengue hémorragique ou un syndrome de choc après une deuxième infection. On pense qu'un biotype de dengue 2 originaire d'Asie du Sud-Est et introduit à Cuba est responsable de l'épidémie de 1981. Les virus de la dengue 2 d'origine caraïbe qui en sont génétiquement distincts et circulaient dans les années 1970 n'ont pas provoqué la maladie.

De quelle manière une deuxième infection par le virus de la dengue entraîne-t-elle une maladie grave? Une étude récente menée en Thaïlande incite à penser que lorsque les anticorps qui subsistent après une première infection sont capables de neutraliser, même faiblement, un deuxième type viral, la deuxième infection se produit effectivement mais sa gravité est amoindrie et la maladie est bénigne. S'il n'y a pas stimulation d'anticorps neutralisants donnant lieu à des réactions croisées, la deuxième infection se trouve alors sous l'influence d'anticorps facilitants et la maladie qui en résulte est grave. Selon l'absence ou la présence des antigènes sur le premier et le deuxième virus, la maladie est plus ou moins grave. La gravité de la maladie pourrait s'expliquer par un autre mécanisme, à savoir que les virus d'Asie du Sud-Est pourraient être intrinsèquement plus enclins à provoquer une infection grave, du fait de la présence d'anticorps facilitants, que les virus originaires d'autres zones géographiques.

La propagation de la dengue hémorragique et du syndrome de choc à de nouvelles régions constitue toujours une occasion d'étudier et de mieux comprendre la pathogénie de la maladie. Dans la plupart des pays, il manque deux éléments importants à la lutte contre la dengue, à savoir une meilleure surveillance de la forme hémorragique et de la forme avec syndrome de choc et une meilleure recherche qui devrait comporter au moins l'étude des sérum pré- et post-épidémiques et l'isolement du virus sur les cas sérologiquement confirmés.

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